PCT/JP 2004/019455
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PCT/JP 2004/019455

Patents Form 1/77

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
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1. Your reference

ADS/PB60633P

2. Patent application number
(The Patent Office will fill this part in)

0329584.7

20 DEC 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Tanabe Seiyaku Co Ltd
2-10 Dosho-Machi 3-Chome
Chuo-Ku
Osaka
Japan

Patents ADP number *(if you know it)*

758987003

If the applicant is a corporate body, give the country/state of its incorporation

Japan

4. Title of the invention

Novel Compounds

5. Name of your agent *(if you have one)*

Helen Quillin

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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980 GREAT WEST ROAD
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80725550006

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months.

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. Divisionals, etc: Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)

Number of earlier UK application	Date of filing *(day / month / year)*

8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request?

YES

Answer YES if:

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

Otherwise answer NO (See note d)

Patents Form 1/77

9. Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

Continuation sheets of this form	
Description	20
Claim(s)	4
Abstract	1
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent (Patents Form 7/77)	
Request for a preliminary examination and search (Patents Form 9/77)	
Request for a substantive examination (Patents Form 10/77)	
Any other documents (please specify)	

11. I/We request the grant of a patent on the basis of this application.

Signature(s) Helen Quillin pp Andrew D. Shaw Date 19 Dec 2003

12. Name, daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

Lesley Wells

Tel. 01438 768599

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PB60633P

Novel Compounds

The present invention relates to novel compounds, processes for their preparation, compositions comprising them and their use in the treatment of diseases capable of being modulated by the inhibition of cell adhesion. More particularly the present invention relates to novel phenylalanine derivatives that inhibit α_4 integrin mediated cell adhesion and which are useful for the treatment of chronic inflammatory diseases.

The multiple adhesive interactions between leukocytes and endothelial cells or extracellular matrix proteins are a key factor in the regulation of immunity and inflammation. The earliest events in the migration of leukocytes out of the vasculature at site of inflammation include leukocyte rolling followed by changes in integrin avidity, which lead to subsequent firm adhesion (for reviews see Butcher, *Cell* 67:1033-1036 (1991); Harlan, *Blood* 3:513-525 (1985); Hemler, *Annu. Rev. Immunol.* 8:365-400 (1990); Osborn, *Cell* 62:3-6 (1990); Shimizu et al., *Immunol. Rev.* 114:109-143 (1990); Springer, *Nature* 346:425-434 (1990); and Springer, *Cell* 76:301-314 (1994)). In response to chemotactic factors, the leukocytes migrate through two adjacent endothelial cells and into tissues that are composed, in part, of the extracellular matrix protein fibronectin (FN) (see Wayner et al., *J. Cell Biol.* 105:1873-1884 (1987)) and collagen (CN) (see Bornstein et al., *Ann. Rev. Biochem.* 49:957-1003 (1980); and Miller, Chemistry of the collagens and their distribution, in "Extracellular Matrix Biochemistry", K.A. Piez and A.H. Reddi, editors, Elsevier, Amsterdam, 41-78 (1983)). Important recognition molecules that participate in these adhesive reactions belong to the integrin gene superfamily (for reviews see Hemler, *Annu. Rev. Immunol.* 8:365-400 (1990); Hynes, *Cell* 48:549-554 (1987); Shimizu et al., *Immunol. Rev.* 114:109-143 (1990); and Springer, *Nature* 346:425-434 (1990)).

Integrins are heterodimers composed of non-covalently associated subunits, referred to as the alpha (α) and beta (β) subunits. To date, 8 integrin β subunits have been identified which can associate with 16 distinct α subunits to form 23 distinct integrins.

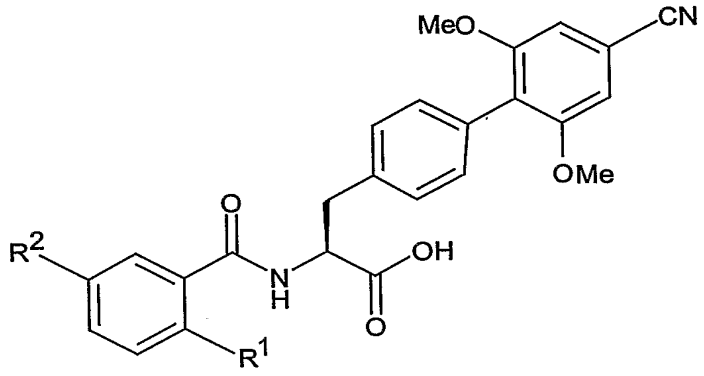
The $\alpha_4\beta_1$ integrin, also known as VLA-4 (Very Late Antigen-4), is constitutively expressed on the surface of leukocytes including lymphocytes, monocytes, eosinophils and basophils (see Hemler et al., *J. Bio. Chem.* 262:11478-11485 (1987); and Bochner et al., *J. Exp. Med.* 173:1553-1556 (1991)). VLA-4 is reported to be present on neutrophils from septic patients (see Ibbotson et al., *Nature Med.* 7:465-470 (2001)). VLA-4 binds to vascular cell adhesion molecule-1 (VCAM-1) on activated endothelial cells, resulting in extravasation of leukocytes (Elices et al., *Cell* 60:577-584 (1990)). Once the cells have

reached the extravascular space, VLA-4 can bind to the connecting segment 1 (CS-1), an alternatively spliced region of the FN A chain (Wayne et al., *J. Cell Biol.* 109:1321-1330 (1989)). In addition, VLA-4 is known to bind to osteopontin, a protein upregulated in arteriosclerotic plaques (see Bayless et al., *J. Cell Science* 111:1165-1174 (1998)).

Also, it has been described that an orally bioavailable, non-peptide small molecule antagonist of α_4 could be useful in treating or preventing conditions such as asthma, inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis and other diseases (see patent applications WO 99/36393 and WO 02/18320, the contents of which are incorporated by reference).

A novel class of compounds has now been discovered which fall within the generic scope of patent application WO 99/36393, but are not specifically disclosed therein, and have been found to exhibit a surprisingly enhanced activity and pharmacokinetic profile.

The present invention therefore provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable derivative thereof



(I)

in which:

R^1 is halogen; and

R^2 is halogen, C_{1-6}alkyl or C_{1-6}alkoxy.

Preferably R^1 is bromo.

Preferably R^2 is halogen, particularly fluoro or C_{1-6}alkoxy, particularly ethoxy.

Throughout the present specification, unless otherwise stated:

the term "halogen" is used to describe a group selected from fluorine, chlorine, bromine or iodine;

the term " C_{1-6}alkyl" is used to describe a group or a part of the group comprising a linear or branched alkyl group containing from 1 to 6 carbon atoms; examples of such groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert butyl, pentyl or hexyl;

the term " C_{1-6}alkoxy" is used to describe a group or a part of the group wherein an oxygen atom is bound to the above mentioned C_{1-6}alkyl group; examples of such groups include methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, isobutoxy, tert butoxy, pentoxy or hexoxy.

Particularly preferred compounds of this invention include Examples E1 - E4 (as described below) or a pharmaceutically acceptable derivative thereof.

The characteristics of the present compounds are the introduction of a cyano group at the 4'-position of the biphenyl nucleus in combination with the claimed 2,5 di- substituted benzoyl group.

The compounds of the present invention have potent inhibitory activity against α_4 integrin mediated cell adhesion, and show excellent bioavailability after oral administration. The compounds of the present invention reduce hepatic clearance thereby improving the systemic exposure.

The compounds of the present invention, therefore, show excellent *in vivo* efficacy against the unfavorable conditions caused by the α_4 integrin mediated cell adhesion.

It will be appreciated that the compounds of formula (I) and their pharmaceutically acceptable derivatives may have more than one asymmetric carbon atoms and therefore may occur as diastereomers. All such isomeric forms are included within the present invention, including mixtures thereof.

Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or HPLC. A single stereoisomeric form of the compound may also be prepared from a corresponding optically pure intermediate or by resolution, such as HPLC of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the

corresponding racemate with a suitable optically active acid or base, as appropriate. Alternatively a mixture of enantiomers may be separated by chemical reaction with an appropriate chiral compound with the formation of a new covalently bonded species, for example the coupling of a racemic carboxylic acid with a chiral amine or alcohol to give a diastereomeric mixture (in the case of amides or esters respectively), which may be separated by conventional techniques such as column chromatography, HPLC or fractional crystallisation. The single diastereomers may then be converted to the single enantiomers of the desired compound by appropriate chemistry such as hydrolytic cleavage of the new covalent bond.

As used herein, the term "pharmaceutically acceptable derivative", means any pharmaceutically acceptable salt, solvate, or prodrug e.g. ester, of a compound of the invention, which upon administration to the recipient is capable of providing (directly or indirectly) a compound of the invention, or an active metabolite or residue thereof. Such derivatives are recognisable to those skilled in the art, without undue experimentation. Nevertheless, reference is made to the teaching of Burger's Medicinal Chemistry and Drug Discovery, 5th Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the extent of teaching such derivatives. Preferred pharmaceutically acceptable derivatives are salts, solvates, esters, carbamates and phosphate esters. Particularly preferred pharmaceutically acceptable derivatives are salts, solvates and esters. Most preferred pharmaceutically acceptable derivatives are salts and esters.

Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallised. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvates of the compound of the invention are within the scope of the invention.

As used herein, the term "prodrug" means a compound which is converted within the body, e.g. by hydrolysis in the blood, into its active form that has medical effects. Pharmaceutically acceptable prodrugs are described in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, and in D. Fleisher, S. Ramon and H. Barbra "Improved oral drug delivery: solubility limitations overcome by the use of prodrugs", Advanced Drug Delivery Reviews (1996) 19(2) 115-130, each of which are incorporated herein by reference.

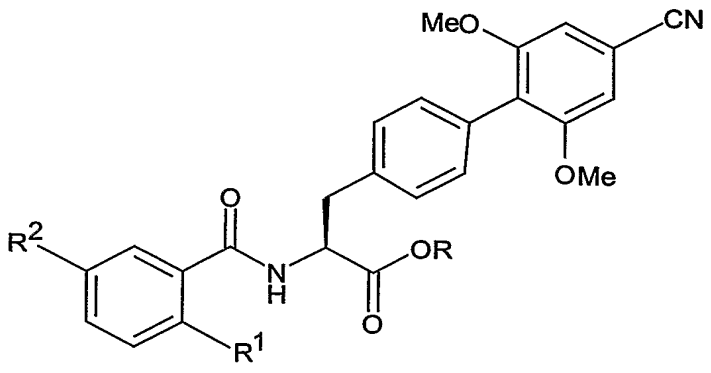
Prodrugs are any covalently bonded carriers that release a compound of formula (I) *in vivo* when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or *in vivo*, yielding the parent compound. In the case of a carboxylic acid (-COOH), esters may be employed, such as methyl esters, ethyl esters, double esters and the like. Esters may be active in their own right and /or be hydrolysable under *in vivo* conditions in the human body. Suitable pharmaceutically acceptable *in vivo* hydrolysable ester groups include those which break down readily in the human body to leave the parent acid or its salt.

The compounds of the present invention may be in the form of and/or may be administered as a pharmaceutically acceptable salt. For a review on suitable salts see Berge et al., J. Pharm. Sci., 1977, 66, 1-19.

Typically, a pharmaceutically acceptable salt may be readily prepared by using a desired acid or base as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

In the case of a compound of formula (I), suitable pharmaceutically acceptable salts are formed from pharmaceutically acceptable bases which include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases, including salts of primary, secondary and tertiary amines, such as isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexyl amine, N-methyl-D-glucamine and tris(hydroxymethyl)methylamine.

In a further aspect, the present invention also provides for a process for the preparation of a compound of formula (I) which comprises hydrolysis of a carboxylic acid ester derivative of formula (II):

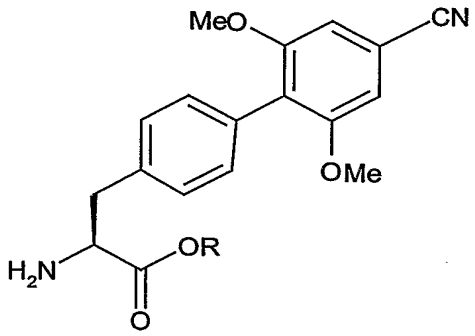


(II)

in which R^1 and R^2 are as defined in formula (I) and R is a group capable of forming a carboxylic acid ester and optionally thereafter forming a pharmaceutically acceptable derivative thereof.

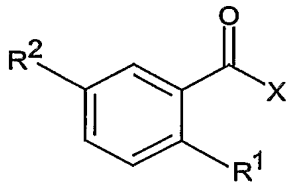
An example of a suitable R group is C_{1-6}alkyl such as methyl or t-butyl, preferably methyl. Hydrolysis may either occur via an acidic or an alkaline medium. Such methods are familiar to those skilled in the art.

The compounds of formula (II) can be prepared by reacting a compound of formula (III) or an acid addition salt thereof:



(III)

in which R is as defined in formula (II) with a compound of formula (IV)



(IV)

in which R^1 and R^2 are as defined in formula (I) and X is a leaving group.

A suitable example of an acid addition salt of the compound of formula (III) is the hydrochloride. A suitable example of a leaving group is halogen, particularly chloro. Reactions between compounds of formula (III) and (IV) are typically carried out in an inert organic solvent such as tetrahydrofuran or dichloromethane or a mixed organic / aqueous system at ambient or elevated temperature in the presence of a suitable base.

Intermediate compounds of formulae (II) and (III) can be prepared by methods described herein. Such intermediate compounds are believed to be novel and form a yet further aspect of this invention.

Intermediate compounds (IV) are either commercially available or can be prepared using methods described herein, by methods known to those skilled in the art or by analogous methods thereto.

Those skilled in the art will appreciate that in the preparation of the compound of the invention or a pharmaceutically acceptable derivative thereof it may be necessary and/or desirable to protect one or more sensitive groups in the molecule to prevent undesirable side reactions. Suitable protecting groups for use according to the present invention are well known to those skilled in the art and may be used in a conventional manner. See, for example, "Protective groups in organic synthesis" by T.W. Greene and P.G.M. Wuts (John Wiley & sons 1991) or "Protecting Groups" by P.J. Kocienski (Georg Thieme Verlag 1994). Examples of suitable amino protecting groups include acyl type protecting groups (e.g. formyl, trifluoroacetyl, acetyl), aromatic urethane type protecting groups (e.g. benzyloxycarbonyl (Cbz) and substituted Cbz), aliphatic urethane protecting groups (e.g. 9-fluorenylmethoxycarbonyl (Fmoc), t-butyloxycarbonyl (Boc), isopropyloxycarbonyl, cyclohexyloxycarbonyl) and alkyl type protecting groups (e.g. benzyl, trityl, chlorotrityl). Examples of suitable oxygen protecting groups may include for example alky silyl groups, such as trimethylsilyl or tert-butyldimethylsilyl; alkyl ethers such as tetrahydropyranyl or tert-butyl; or esters such as acetate.

Compounds of this invention may be tested for *in vitro* biological activity in accordance with the following assay.

Jurkat J6 Scintillation Proximity Assay (SPA)

The Jurkat J6 Scintillation Proximity Assay was used to investigate the interaction of the integrin VLA-4 (Very Late Antigen-4; 41; CD49d, CD29) expressed on the Jurkat J6 cell

membrane with test compounds. J6 cells (1 million cells/well) were allowed to coat wheat germ agglutinin coated SPA beads (Amersham, 1mg/well) in assay buffer containing 50mM HEPES, 100mM NaCl and 1mM MnCl2 (pH with 4M NaOH to 7.5). Tritiated 3H Standard Compound A (1-3 nM final assay concentration) and test compounds were dissolved in an appropriate solvent and diluted in assay buffer. Compounds were assayed in duplicate, a four parameter curve fit being applied. The equilibrium dissociation constant for each compound was calculated according to the method of Cheng & Prusoff. Data were presented as the mean pKi.

Standard compound A is (2S)-3-[4-({[4-(aminocarbonyl)-1-piperidinyl]carbonyl}oxy)phenyl]-2-[((2S)-4-methyl-2-{[2-(2-methylphenoxy)acetyl]amino}pentanoyl)amino] propanoic acid potassium salt which is described in patent application WO 00/37444 (Glaxo Group Ltd. et al.). Tritiated 3H derivatives may be prepared employing conventional methods.

All examples prepared in accordance with this invention were tested in accordance with this procedure and were found to have a pKi ≥ 8.9.

Compounds of formula (I) and their pharmaceutically acceptable derivatives inhibit α_4 integrin mediated cell adhesion and are believed to be of potential use in the treatment or prophylaxis of such conditions as rheumatoid arthritis (RA); asthma; allergic conditions such as rhinitis; adult respiratory distress syndrome; AIDS-dementia; Alzheimer's disease; cardiovascular diseases; thrombosis or harmful platelet aggregation; reocclusion following thrombolysis; reperfusion injury; skin inflammatory diseases such as psoriasis, eczema, contact dermatitis and atopic dermatitis; diabetes (e.g., insulin-dependent diabetes mellitus, autoimmune diabetes); multiple sclerosis; systemic lupus erythematosus (SLE); inflammatory bowel disease such as ulcerative colitis, Crohn's disease (regional enteritis) and pouchitis (for example, resulting after proctocolectomy and ileoanal anastomosis); diseases associated with leukocyte infiltration to the gastrointestinal tract such as Celiac disease, nontropical Sprue, enteropathy associated with seronegative arthropathies, lymphocytic or collagenous colitis, and eosinophilic gastroenteritis; diseases associated with leukocyte infiltration to other epithelial lined tissues, such as skin, urinary tract, respiratory airway, and joint synovium; pancreatitis; mastitis (mammary gland); hepatitis; cholecystitis; cholangitis or pericholangitis (bile duct and surrounding tissue of the liver); bronchitis; sinusitis; inflammatory diseases of the lung which result in interstitial fibrosis, such as hypersensitivity pneumonitis; collagen disease (in SLE and RA); sarcoidosis; osteoporosis; osteoarthritis; atherosclerosis; neoplastic diseases including metastasis of

neoplastic or cancerous growth; wound (wound healing enhancement); certain eye diseases such as retinal detachment, allergic conjunctivitis and autoimmune uveitis; Sjogren's syndrome; rejection (chronic and acute) after organ transplantation; host vs. graft or graft vs. host diseases; intimal hyperplasia; arteriosclerosis (including graft arteriosclerosis after transplantation); reinfarction or restenosis after surgery such as percutaneous transluminal coronary angioplasty (PTCA) and percutaneous transluminal artery recanalization; nephritis; tumor angiogenesis; malignant tumor; multiple myeloma and myeloma-induced bone resorption; sepsis; and central nervous system injury such as stroke, traumatic brain injury and spinal cord injury and Meniere's disease.

The compounds of the present invention can be preferably used for the treatment or prevention of asthma, allergic conditions such as rhinitis, inflammatory bowel disease such as ulcerative colitis and Crohn's disease, rheumatoid arthritis, atopic dermatitis, multiple sclerosis and rejection after organ transplantation.

The present invention further provides for a method for the treatment or prophylaxis of conditions in which an inhibitor of α_4 integrin mediated cell adhesion is beneficialwhich comprises administering to a patient in need thereof a safe and effective amount of a compound of formula (I). The present invention especially provides for a method for the treatment or prophylaxis of the aforementioned conditions.

The present invention also provides for a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in therapy, particularly the treatment of the aforementioned disorders.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable derivative in the manufacture of a medicament for the treatment or prophylaxis of conditions in which an inhibitor of α_4 integrin mediated cell adhesion is beneficial, particularly the aforementioned disorders.

While it is possible for the compounds of the present invention to be administered alone, it is preferable to formulate into a pharmaceutical composition in accordance with standard pharmaceutical practice. Thus the invention also provides for a pharmaceutical composition which comprises a therapeutically effective amount of a compound of formula (I) in admixture with a pharmaceutically acceptable carrier or diluent.

The invention further provides for a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with another therapeutically active agent.

There is further provided by the present invention a process of preparing a pharmaceutical composition, which process comprises mixing at least one compound of the invention or a pharmaceutically acceptable derivative thereof, together with a pharmaceutically acceptable carrier or diluent.

The pharmaceutical compositions may be for human or animal usage in human and veterinary medicine and will typically comprise any one or more of a pharmaceutically acceptable diluent, carrier or excipient. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R. Gennaro edit. 1985). The choice of pharmaceutical carrier, excipient or diluent can be selected with regard to the intended route of administration and standard pharmaceutical practice. The carrier or diluent must be acceptable in the sense of being not deleterious to the recipient thereof. The pharmaceutically acceptable carrier or diluent may be, for example, binders (e.g., syrup, gum arabic, gelatin, sorbitol, tragacanth, polyvinylpyrrolidone), excipients (e.g., lactose, sucrose, corn starch, potassium phosphate, sorbitol, glycine), lubricants (e.g., magnesium stearate, talc, polyethylene glycol, silica) disintegrators (e.g., potato starch), wetting agents (e.g., sodium laurylsulfate), and the like.

The routes for administration (delivery) of the composition of the invention include, but are not limited to, one or more of: oral (e. g. as a tablet, capsule, or as an ingestible solution), topical, mucosal (e. g. as a nasal spray or aerosol for inhalation), nasal, parenteral (e. g. by an injectable form), gastrointestinal, intraspinal, intraperitoneal, intramuscular, intravenous, intrauterine, intraocular, intradermal, intracranial, intratracheal, intravaginal, intracerebroventricular, intracerebral, subcutaneous, ophthalmic (including intravitreal or intracameral), transdermal, rectal, buccal, epidural, sublingual.

For example, the compound can be administered orally in the form of tablets, capsules, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications. The tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch

glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included. Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the agent may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

The compounds of the invention may be milled using known milling procedures such as wet milling to obtain a particle size appropriate for tablet formation and for other formulation types. Finely divided (nanoparticulate) preparations of the compounds of the invention may be prepared by processes known in the art, for example see International Patent Application No. WO 02/00196 (SmithKline Beecham).

If the compound of the present invention is administered parenterally, then examples of such administration include one or more of: intravenously, intraarterially, intraperitoneally, intrathecally, intraventricularly, intraurethrally, intrasternally, intracranially, intramuscularly or subcutaneously administering the agent; and/or by using infusion techniques. For parenteral administration, the compounds are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

As indicated, the compound of the present invention can be administered intranasally or by inhalation and is conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray or nebuliser with the use of a suitable propellant, e. g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134AT™) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray or nebuliser may contain a solution or suspension of the active compound, e. g. using a

mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e. g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound and a suitable powder base such as lactose or starch.

Alternatively, the compound of the present invention can be administered in the form of a suppository or pessary, or it may be applied topically in the form of a gel, hydrogel, lotion, solution, cream, ointment or dusting powder. The compound of the present invention may also be dermally or transdermally administered, for example, by the use of a skin patch. They may also be administered by the pulmonary or rectal routes. They may also be administered by the ocular route. For ophthalmic use, the compounds can be formulated as micronised suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzylalkonium chloride. Alternatively, they may be formulated in an ointment such as petrolatum.

For application topically to the skin, the agent of the present invention can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, it can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

The compositions of the present invention may be administered by direct injection.

In a preferred embodiment, the agents of the present invention are delivered systemically (such as orally, buccally, sublingually), more preferably orally.

Hence, preferably the agent is in a form that is suitable for oral delivery.

Typically, a physician will determine the actual dosage which will be most suitable for an individual subject. The specific dose level and frequency of dosage for any particular individual may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of

administration, rate of excretion, drug combination, the severity of the particular condition, and the individual undergoing therapy.

For oral and parenteral administration to humans, the daily dosage level of the agent may be in single or divided doses.

A proposed dose of the compounds according to the present invention for administration to a human (of approximately 70kg body weight) is 0.1mg to 1g, preferably to 1mg to 500mg of the active ingredient per unit dose, expressed as the weight of free acid. The unit dose may be administered, for example, 1 to 4 times per day. The dose will depend on the route of administration. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient as well as the severity of the condition to be treated. The dosage will also depend on the route of administration. The precise dose and route of administration will ultimately be at the discretion of the attendant physician or veterinarian.

The compounds of the invention may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound of the invention or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent.

When a compound of the invention or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art. It will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. Examples of other active agents that may be combined with a compound of formula (I) include, but not limited to: (a) other VLA-4 antagonists; (b) H1 histamine antagonists; (c) NSAID's; (d) anti-diabetic agent e.g. glitazones (e) anti-cholinergic agents (f) COX-2 inhibitors; (g) PDE-IV inhibitors; (h) steroids e.g. corticosteroids; (i) beta agonists; (j) antagonists of the chemokine receptors e.g. CCR-2, CCR-3, CCR-5 and CCR-8; (k) suitable multiple sclerosis agents such as interferon; and (l) LFA-1 antagonists.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a

combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations by any convenient route. When administration is sequential, either the compound of the invention or the second therapeutic agent may be administered first. When administration is simultaneous, the combination may be administered either in the same or different pharmaceutical composition.

When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation. When formulated separately they may be provided in any convenient formulation, conveniently in such manner as are known for such compounds in the art.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1
(S)-2-*tert*-Butoxycarbonylamino-3-(4-hydroxyphenyl)propionic acid methyl ester (D1)

Di-*tert*-butyl dicarbonate (200 g, 0.92 mol) was added portionwise to a mixture of L-tyrosine methyl ester hydrochloride (200 g, 0.86 mol) and sodium hydrogen carbonate (100 g, 1.19 mol) in dichloromethane (1 L) and water (1 L). The mixture was stirred for 2 hours at room temperature. The organic layer was separated and the aqueous phase re-extracted with dichloromethane (500 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure to yield the crude title compound as a colourless glass, which was used in the following step without purification; LC/MS (ES-ve): $[M-H]^-$ at m/z 294 ($C_{15}H_{21}NO_5$ requires $[M-H]^-$ at m/z 294).

Description 2
(S)-2-*tert*-Butoxycarbonylamino-3-(4-trifluoromethanesulfonyloxyphenyl)propionic acid methyl ester (D2)

Pyridine (58 mL, 0.72 mol) was added to a solution of crude (S)-2-*tert*-butoxycarbonylamino-3-(4-hydroxyphenyl)propionic acid methyl ester (D1, 70.5 g, 0.24 mol) in dichloromethane (1 L) under argon. The solution was cooled in ice, and then trifluoromethanesulfonic anhydride (52 mL, 0.31 mol) was added dropwise with stirring. After the addition was complete, the mixture was stirred in ice for 2 hours, washed with 2M hydrochloric acid (500 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (Biotage 75L, 800 g silica) eluting with ethyl acetate:hexane (15:85) to yield the title compound as a colourless oil which slowly solidified to give a white solid; LC/MS (ES+ve): $[M\text{-}BOC+H]^+$ at m/z 328 ($C_{16}H_{20}NO_7S$ requires $[M+H]^+$ at m/z 428).

Description 3

4-Hydroxymethyl-2,6-dimethoxyphenylboronic acid (D3)

A solution of (3,5-dimethoxyphenyl)methanol (53 g, 0.31 mol) in dry tetrahydrofuran (1 L) was cooled to –50°C to –70°C under argon and treated with n-butyllithium (450 mL, 1.6M in hexane, 0.72 mol) over 30 minutes. After the addition, the reaction mixture was allowed to warm to 0°C over 45 minutes and then left to stand at room temperature for 2 hours. The reaction was subsequently re-cooled to –60°C and treated with trimethylborate (135 mL, 1.15 mol) portionwise. Following the addition, the mixture was allowed to warm to room temperature and stirred for a further 18 hours. The reaction was quenched at 0°C by the portionwise addition of an aqueous solution of citric acid (75 g of citric acid in 300 mL of water). The aqueous layer was saturated by the addition of sodium chloride and the product extracted with ethyl acetate (2 x 1 L). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. Ethyl acetate (100 mL) was added to the residue and the resulting colourless precipitate collected by filtration and dried at 40°C under vacuum to yield the title compound as a colourless solid which was used in the following reaction without purification.

Description 4

(S)-2-*tert*-Butoxycarbonylamino-3-(4'-hydroxymethyl-2',6'-dimethoxybiphenyl-4-yl)propionic acid methyl ester (D4)

Triethylamine (28 mL, 0.20 mol) was added to a solution of 2-(S)-*tert*-butoxycarbonylamino-3-(4-trifluoromethanesulfonyloxyphenyl)propionic acid methyl ester (D2, 42.73 g, 0.10 mol) and 4-hydroxymethyl-2,6-dimethoxyphenyl boronic acid (D3, 29.7 g, 0.14 mol) in dry dimethylformamide (250 mL). After degassing with argon, tetrakis(triphenylphosphine)palladium (0) (5.8 g, 5 mmol) was added and the mixture was

heated at 90°C for 1 hour under argon. [NB A slight exotherm was observed]. After allowing to cool to room temperature, the mixture was diluted with ethyl acetate (1 L) and water (700 mL), and separated. The organic layer was washed with water (2 x 300 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (Biotage 75L, 800 g silica) eluting with ethyl acetate:hexane (50:50) to yield the title compound as a colourless solid; LC/MS (ES+ve): $[M\text{-}BOC+H]^+$ at m/z 346 ($C_{24}H_{31}NO_7$ requires $[M+H]^+$ at m/z 446).

Description 5

(S)-2-*tert*-Butoxycarbonylamino-3-(4'-formyl-2',6'-dimethoxybiphenyl-4-yl)propionic acid methyl ester (D5)

Manganese dioxide (230 g, 2.64 mol) was added portionwise to a solution of (S)-2-*tert*-butoxycarbonylamino-3-(4'-hydroxymethyl-2',6'-dimethoxybiphenyl-4-yl)propionic acid methyl ester (D4, 28.98 g, 65.1 mmol) in dichloromethane (1 L). The resulting suspension was stirred at room temperature for 1 hour and then filtered through celite, washing the celite pad with further dichloromethane (1 L). The filtrate was concentrated at reduced pressure to yield the product as a colourless foam which was used without further purification; LC/MS (ES+ve): $[M\text{-}BOC+H]^+$ at m/z 344 ($C_{24}H_{29}NO_7$ requires $[M+H]^+$ at m/z 444).

Description 6

(S)-2-*tert*-Butoxycarbonylamino-3-[4'-(hydroxyiminomethyl)-2',6'-dimethoxybiphenyl-4-yl]propionic acid methyl ester (D6)

Hydroxylamine hydrochloride (7.4 g, 106 mmol) and diisopropylethylamine (18 mL, 106 mmol) were added to a solution of (S)-2-*tert*-butoxycarbonylamino-3-(4'-formyl-2',6'-dimethoxybiphenyl-4-yl)propionic acid methyl ester (D5, 23.6 g, 53 mmol) in tetrahydrofuran (300 mL). The reaction mixture was heated at reflux for 2 hours and then allowed to cool to room temperature. The solution was concentrated at reduced pressure and then redissolved in ethyl acetate (500 mL), washed with 10% aqueous citric acid, water and brine (500 mL each), dried over magnesium sulfate, filtered and concentrated under reduced pressure to yield a colourless foam, which was used in the next step without further purification; LC/MS (ES+ve): $[M\text{-}BOC+H]^+$ at m/z 359 ($C_{24}H_{30}N_2O_7$ requires $[M+H]^+$ at m/z 459).

Description 7

(S)-2-Amino-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid methyl ester hydrochloride (D7)

Thionyl chloride (30 mL, 411 mmol) was added dropwise to a solution of (S)-2-*tert*-butoxycarbonylamino-3-[4'-(hydroxyiminomethyl)-2',6'-dimethoxybiphenyl-4-yl]propionic acid methyl ester (D6, 46.5 g, 101 mmol) in dichloromethane (500 mL) at 0°C under argon. The reaction was allowed to warm to room temperature and stirred for 3 days. The precipitated solid was collected by filtration, washed with dichloromethane (200 mL) and dried at 45°C under reduced pressure. The title compound was isolated as a white solid; LC/MS (ES+ve): $[M+H]^+$ at m/z 341 ($C_{19}H_{2d}N_2O_4$ requires $[M+H]^+$ at m/z 341).

Description 8

2-Bromo-5-hydroxybenzoic acid methyl ester (D8)

2-Bromo-5-methoxybenzoic acid (30.0 g, 130 mmol) was stirred under argon in dry dichloromethane (600 mL), cooled in dry ice / acetone, as boron tribromide (1M in dichloromethane, 280 mL, 280 mmol) was added over 15 minutes. The mixture was then stirred at ambient temperature for 2.5 hours, yielding a precipitate. Methanol (300 mL) was then cautiously added dropwise (CARE: initially strongly exothermic, and with effervescence) over 30 minutes, finally giving a dark homogeneous solution, to which was added concentrated sulphuric acid (15 mL). The solution was stirred at reflux for 1 hour, cooled, and concentrated under reduced pressure. The residue was dissolved in dichloromethane (500 mL), washed with brine (500 mL), dried over magnesium sulfate, filtered and concentrated at reduced pressure to yield the title compound as a solid; LC/MS (ES+ve): $[M+H]^+$ at m/z 231, 233 ($C_8H_7BrO_3$ requires $[M+H]^+$ at m/z 231, 233).

Description 9

2-Bromo-5-ethoxybenzoic acid methyl ester (D9)

Sodium hydride (60% in mineral oil, 4.24 g, 106 mmol) was stirred under argon in dry dimethylformamide (150 mL), cooling in ice, as 2-bromo-5-hydroxybenzoic acid methyl ester (D8, 20.41 g, 88 mmol) was added in dry dimethylformamide (150 mL) over 15 minutes. The mixture was stirred at ambient temperature for 45 minutes, re-cooled in ice, and treated with iodoethane (8.5 mL, 106 mmol). This mixture was stirred at ambient temperature for 3 hours, concentrated at reduced pressure, diluted with ethyl acetate (400 mL), washed with water (3 x 400 mL) and brine (400 mL), dried over magnesium sulfate, filtered and concentrated at reduced pressure to yield the title compound, contaminated with a trace of the corresponding ethyl ester, and residual mineral oil. This material was used in the next step without further purification; LC/MS (ES+ve): $[M+H]^+$ at m/z 259, 261 ($C_{10}H_{11}BrO_3$ requires $[M+H]^+$ at m/z 259, 261).

Description 10

2-Bromo-5-ethoxybenzoic acid (D10)

2-Bromo-5-ethoxybenzoic acid methyl ester (D9, 20.53 g, 79 mmol) was stirred in tetrahydrofuran (600 mL), and treated with lithium hydroxide (18.2 g, 791 mmol) in water (200 mL). The mixture was stirred for 4 days, concentrated at reduced pressure, diluted with water (500 mL), acidified with 5N hydrochloric acid, and extracted into ethyl acetate (2 x 300 mL). The combined extracts were washed with brine (250 mL), dried over magnesium sulfate, filtered and concentrated at reduced pressure to give an off-white solid. Trituration with hexane, filtration and drying gave the title compound as a white powder; LC/MS (ES+ve): $[M+H]^+$ at m/z 245, 247 ($C_9H_9BrO_3$ requires $[M+H]^+$ at m/z 245, 247).

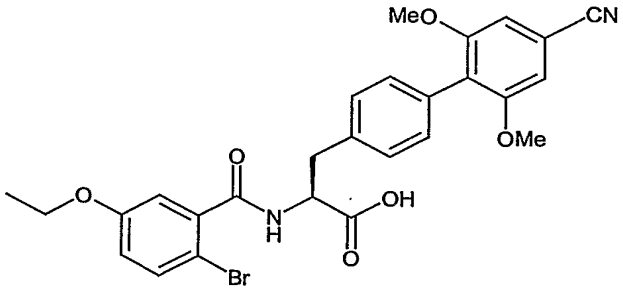
Description 11

(S)-2-{[1-(2-Bromo-5-ethoxyphenyl)methanoyl]amino}-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid methyl ester (D11)

2-Amino-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid methyl ester hydrochloride (D7, 37.1 g, 98.5 mmol) was dissolved in dichloromethane (500 mL) and water (400 mL) and cooled to 0°C under argon. Sodium hydrogen carbonate (20.1 g, 239.3 mmol) was added to the reaction mixture followed by the dropwise addition of 2-bromo-5-ethoxybenzoyl chloride (27.2 g, 103.7 mmol) {prepared from 2-bromo-5-ethoxybenzoic acid D10 by standard procedures using oxalyl chloride (4 equiv.) in dichloromethane and a drop of dimethylformamide}. The reaction was stirred at 0°C for 1 hour and was then diluted with a saturated aqueous solution of sodium hydrogen carbonate (200 mL). After separation of the organic layer, the aqueous layer was re-extracted with dichloromethane (2 x 400 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated at reduced pressure. The product was purified by silica gel chromatography (Biotage 75L, 800 g silica) eluting with ethyl acetate: dichloromethane (3:97) to yield the title compound as a colourless solid; MS (ES+ve): $[M+H]^+$ at m/z 567, 569 ($C_{28}H_{27}BrN_2O_6$ requires $[M+H]^+$ at m/z 567, 569).

Example 1

(S)-2-{[1-(2-Bromo-5-ethoxyphenyl)methanoyl]amino}-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid (E1)



A solution of (S)-2-{[1-(2-Bromo-5-ethoxyphenyl)methanoyl]amino}-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid methyl ester (D11, 51.5 g, 90.8 mmol) in tetrahydrofuran (950 mL) was cooled to 0°C and treated with 0.5M aqueous lithium hydroxide (700 mL). The reaction mixture was stirred at 0°C for 1 hour and then acidified with 5M hydrochloric acid. The tetrahydrofuran was evaporated *in vacuo* and the residue was diluted with ethyl acetate. After separation of the organic layer, the aqueous phase was re-extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate and the solvent was evaporated *in vacuo* to yield the title compound as a colourless solid;

^{1}H NMR δ (DMSO-d6): 1.29 (3H, t, *J* 7.0Hz), 2.96 (1H, dd, *J* 13.9, 10.9Hz), 3.22 (1H, dd, *J* 14.1, 4.2Hz), 3.71 (6H, s), 3.99 (2H, q, *J* 7.0Hz), 4.65 (1H, ddd, *J* 10.9, 8.4, 4.3Hz), 6.69 (1H, d, *J* 3.0Hz), 6.91 (1H, dd, *J* 8.8, 3.1Hz), 7.14 (2H, d, *J* 8.1Hz), 7.24 (2H, s), 7.32 (2H, d, *J* 8.1Hz,), 7.47 (1H, d, *J* 8.8Hz), 8.77 (1H, br. d, *J* 8.4Hz), 12.83 (1H, br. s); MS (ES+ve) $[M+H]^+$ at m/z 553, 555 ($C_{27}H_{25}BrN_2O_6$ requires $[M+H]^+$ at m/z 553, 555).

Example 2

(*S*)-2-{[1-(2-Bromo-5-fluorophenyl)methanoyl]amino}-3-(4'-cyano-2'6'-dimethoxybiphenyl-4-yl)propionic acid (E2)

Prepared in an analogous manners to those of D11 and E1 using D7 and 2-bromo-5-fluorobenzoyl chloride (from Apollo). $[M+H]^+$ at m/z 527, 529

Example 3

(*S*)-2-{[1-(2-Bromo-5-methoxyphenyl)methanoyl]amino}-3-(4'-cyano-2'6'-dimethoxybiphenyl-4-yl)propionic acid (E3)

Prepared in an analogous manners to those of D11 and E1 using D7 and 2-bromo-5-methoxybenzoyl chloride for E3 (from Avocado). $[M+H]^+$ at m/z 539, 541

Example 4

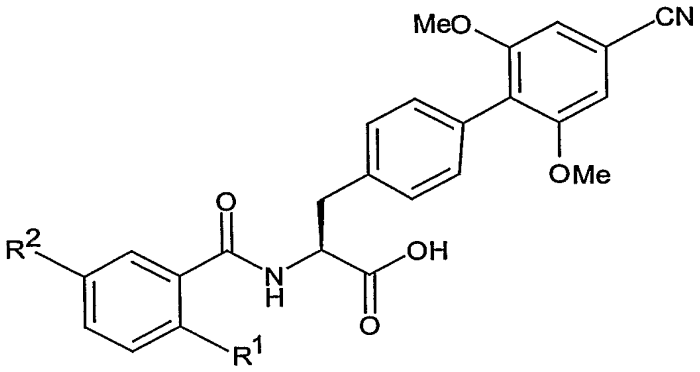
(*S*)-2-{[1-(2-Bromo-5-methylphenyl)methanoyl]amino}-3-(4'-cyano-2'6'-dimethoxybiphenyl-4-yl)propionic acid (E4)

Prepared in an analogous manners to those of D11 and E1 using D7 and bromo-5-methylbenzoyl chloride (prepared from 2-bromo-5-methylbenzoic acid (from Apin) which is converted to the acid chloride by standard methods, e.g. stirring at room temperature in dichloromethane with excess oxalyl chloride and a drop of dimethylformamide).

$[M+H]^+$ at m/z 523, 525

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable derivative thereof



(I)

in which:
R^1 is halogen; and
R^2 is halogen, C_{1-6}alkyl or C_{1-6}alkoxy.

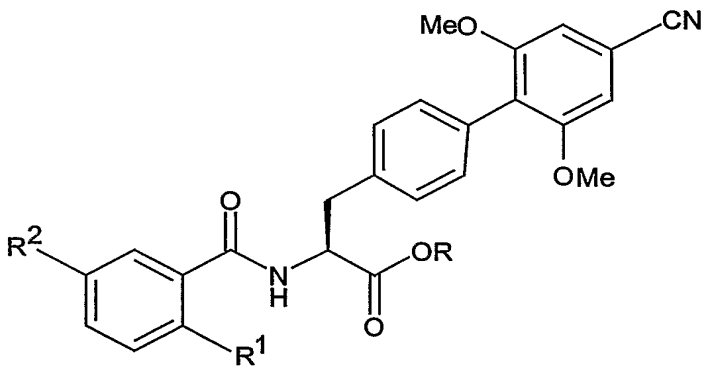
2. A compound according to claim 1 in which R^1 is bromo.

3. A compound according to claim 1 or 2 in which R^2 is halogen or C_{1-6}alkoxy.

4. A compound according to claim 3 in which R^2 is fluoro or ethoxy.

5. A compound according to claim 1 which is selected from the group consisting of:
(S)-2-{[1-(2-Bromo-5-ethoxyphenyl)methanoyl]amino}-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid;
(*S*)-2-{[1-(2-Bromo-5-fluorophenyl)methanoyl]amino}-3-(4'-cyano-2'6'-dimethoxybiphenyl-4-yl)propionic acid;
(*S*)-2-{[1-(2-Bromo-5-methoxyphenyl)methanoyl]amino}-3-(4'-cyano-2'6'-dimethoxybiphenyl-4-yl)propionic acid;
(*S*)-2-{[1-(2-Bromo-5-methylphenyl)methanoyl]amino}-3-(4'-cyano-2'6'-dimethoxybiphenyl-4-yl)propionic acid)
or a pharmaceutically acceptable derivative thereof.

6. A process for the preparation of a compound of formula (I) which comprises hydrolysis of a carboxylic acid ester derivative of formula (II):



(II)

in which R^1 and R^2 are as defined in formula (I) and R is a group capable of forming a carboxylic acid ester and optionally thereafter forming a pharmaceutically acceptable derivative thereof.

7. A compound according to any one of claims 1 to 5 for use in therapy.

8. A pharmaceutical composition which comprises a therapeutically effective amount of a compound according to any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier or diluent.

9. A pharmaceutical composition comprising a compound according to any one of claims 1 - 5 or a pharmaceutically acceptable derivative thereof together with another therapeutically active agent.

10. The use of a compound according to any one of claims 1 to 5 in the manufacture of a medicament for use in the treatment or prophylaxis of conditions in which an inhibitor of α_4 integrin mediated cell adhesion is beneficial.

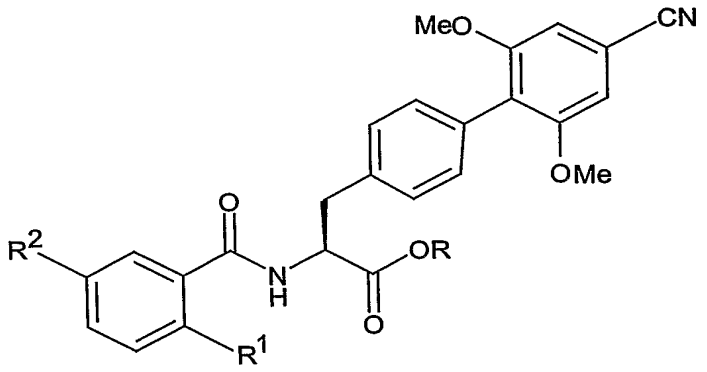
11. A method for the treatment or prophylaxis of conditions in which an inhibitor of α_4 integrin mediated cell adhesion is beneficial which comprises administering to a patient in need thereof a safe and effective amount of a compound according to any one of claims 1 to 5.

12. The method according to claim 11, wherein said condition is selected from the group consisting of rheumatoid arthritis; asthma; allergic conditions; adult respiratory distress syndrome; AIDS-dementia; Alzheimer's disease; cardiovascular diseases; thrombosis or harmful platelet aggregation; reocclusion following thrombolysis;

reperfusion injury; skin inflammatory diseases; diabetes; multiple sclerosis; systemic lupus erythematosus; inflammatory bowel disease; diseases associated with leukocyte infiltration to the gastrointestinal tract; diseases associated with leukocyte infiltration to epithelial lined tissues; pancreatitis; mastitis; hepatitis; cholecystitis; cholangitis or pericholangitis; bronchitis; sinusitis; inflammatory diseases of the lung; collagen disease; sarcoidosis; osteoporosis; osteoarthritis; atherosclerosis; neoplastic diseases; wound; eye diseases; Sjogren's syndrome; rejection after organ transplantation; host vs. graft or graft vs. host diseases; intimal hyperplasia; arteriosclerosis; reinfarction or restenosis after surgery; nephritis; tumor angiogenesis; malignant tumor; multiple myeloma and myeloma-induced bone resorption; sepsis, central nervous system injury and Meniere's disease.

13. The method according to claim 12, wherein said condition is asthma, allergic conditions, inflammatory bowel disease, rheumatoid arthritis, atopic dermatitis, multiple sclerosis or rejection after organ transplantation.

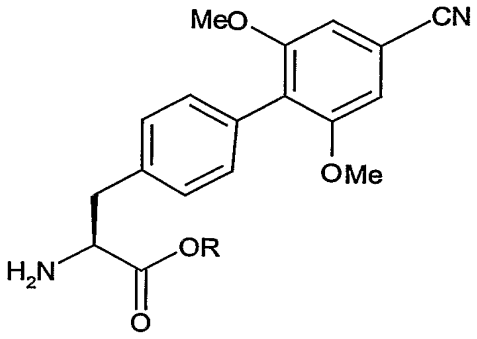
14. A compound of formula (II)



(II)

in which R^1 and R^2 are as defined in formula (I) and R is a group capable of forming a carboxylic acid ester.

15. A compound of formula (III) or an acid addition salt thereof



(III)

in which R is a group capable of forming a carboxylic acid ester.

ABSTRACT

The present invention relates to novel phenylalanine compounds, processes for their preparation, compositions comprising them and their use in the treatment of diseases capable of being modulated by the inhibition of cell adhesion.